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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,714	03/05/2002	Isabelle Mansuy	64481/JPW/AJM/MML	7463

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,714	MANSUY ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *11-20 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed February 1, 2005 has been entered. Applicants' election with traverse of Group I, Claims 1-10, in the response filed February 1, 2005 is acknowledged. The elected invention is drawn to a transgenic nonhuman mammal comprising a transgene as recited in the claims, wherein the transgene is present in germline **and** somatic cells (e.g., an animal generated by transgenesis). The traversal is on the grounds that there would be no serious burden in searching and examining all 6 inventions together. This is not found persuasive because the inventions are separately classified which is a *prima facie* showing of an undue search burden. The searches for the inventions of Groups I-VI are not coextensive. Furthermore, a burden statement has already been presented in the Office Action of 12/30/04, at page 8.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-34 are pending in the instant application.

Claims 11-20 and 31-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **with** traverse in the response filed February 1, 2005.

Accordingly, Claims 1-10 and 21-30 are examined herein. Claims 1-10 cover multiple distinct inventions and are examined herein only to the extent that they encompass the elected subject matter. Claims 21-30 are linking claims.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

The Post Office Address of Eric Kandel has been omitted.

Claim Objections

Claims 1-10 are objected to for encompassing subject matter that goes beyond the elected invention. The elected invention is drawn to a transgenic nonhuman mammal comprising a transgene as recited in the claims, wherein the transgene is present in germline **and** somatic cells (e.g., an animal generated by transgenesis). The claims also cover transgenic animals comprising the transgene in somatic cells, but not in germline cells (e.g. an animal generated by *in vivo* somatic cell genetic modification or by transplantation of genetically modified cells), which is the subject matter of Group II. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims cover humans comprising the nucleic acids recited in the claims, which is non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-10 and 21-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic nonhuman mammal comprising a transgene as recited in the claims, wherein the transgene is present in germline **and** somatic cells (e.g., an animal generated by transgenesis). The transgenes provide for regulated expression of a "heterologous nucleic acid sequence encoding a protein" in a manner that is inducible.

Claims 21-30 cover both transgenic animals comprising the recited transgenes, as well as other types of compositions such as cells and nucleic acid constructs.

The specification fails to provide an enabling disclosure for the claimed transgenic mammals because the use of a transgenic mammal is dependent upon the particular phenotype of the animal, which is dependent on the particular transgene being expressed in the animal as well as a host of other factors. However, the specification does not disclose the phenotype of any transgenic animal having a genetic modification as recited in the claims. Absent a useful phenotype, the skilled artisan would not know how to use the claimed mammals. The specification does not teach a specific phenotypic alteration as a result of the wide variety of genetic modifications covered by the claims. The claimed invention covers transgenic mammals having no phenotypic alteration, or having any phenotype whatsoever. However, the phenotype of a transgenic animal cannot be predicted for the reasons discussed herein below. Thus,

absent a known useful phenotype, the skilled artisan would not know how to use the claimed transgenic mammals.

The specification fails to provide an enabling disclosure for the claimed transgenic mammals because, absent a known useful phenotype, the specification does not disclose how to use the animals. The mere capability to perform gene transfer in various species is not enabling for the claimed methods because the desired phenotype cannot be predictably achieved by simply introducing any construct into the genome. While gene transfer techniques are well-developed for a number of species, including the mouse, methods for achieving the desired level of gene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression vary from species to species. Thus, a construct that confers the desired phenotype in a mouse cannot necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Thus, in the absence of any working examples, the existence of any phenotypic alteration resulting from the genetic modifications of the type claimed in any species of mammal, is highly unpredictable. Given the lack of working examples

and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic mammals.

While the species-specific requirements for transgene design are not clearly understood, examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to use the full scope of the claimed compositions without undue experimentation. The claims cover transgenic mammals expressing any heterologous protein, but the specification does not teach how to use the wide variety of animals covered by the claims. In the absence of disclosure of a useful phenotype, undue experimentation would have been required to make and use the claimed compositions, particularly over the full scope.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your

questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER